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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,597	10/31/2003	Leonard G. Presta	39766-0033CP2C2-C1	1656

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,597	PRESTA ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-11* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/10/07 has been entered.

Applicant cancels claim 12.

Accordingly, claims 6-9, a method for detecting malignancy, comprising detecting the over-or under-expression of the ligand NT-4/5 (SEQ ID NO:45), using its receptor, SEQ ID NO:2, the truncated form thereof, SEQ ID NO:4, or an immunoadhesin thereof, are examined in the instant application.

The embodiment of claims 6-9, as drawn to a method of diagnosis of a pathological condition, by detecting the expression of BDNF (SEQ ID NO:42), NT-3 (SEQ ID NO:43) and NT-4 (SEQ ID NO:44), have been withdrawn from consideration as being drawn to non-elected invention.

Withdrawn Rejection

The full 112, first paragraph, written description, the 112, first paragraph, enablement, item B, concerning essential material, have been withdrawn in view of the amendment.

Restriction

The response asserts that the neurotrophic lactor of the present claims is selected from the group consisting of BDNF (SEQ ID NO: 42), NT-3 (SEQ ID NO:43), NT-4 (SEQ ID NO: 44) and NT-4/5 (SEQ ID NO: 45) and is capable of binding a human trkB receptor polypeptide of SEQ ID NO:2 or SEQ ID NO:4 or an immunoadhesin thereof. The response asserts that the claims include the (withdrawn) neurotrophins BDNF and NT-3 since, per page 2, lines 12-14 of the Office Action mailed October 24, 2006, upon allowance of claim 6 with regard to NT-4 and NT- 4/5, the claims may be examined with respect to BDNF and NT-3 as well. The response concludes that thus, the USPTO's recitation of the requirements of the claims is in error where it suggests that NT-4 or NT-4/5 are somehow different than "a neurotrophic factor" when, in fact, they are each individual members of the group of neurotrophic factors which may satisfy the requirements of the claimed invention.

The response has been considered but is not found to be persuasive for the following reasons:

Applicant did not elect, nor the specification suggests or discloses diagnosis of malignancy by detecting over- or underexpression of a combination of different neurotrophic factors, using the trB receptor. Although the different neurotrophic factors belong to the same family of neurotrophin proteins, they are structurally and functionally different. The different methods of detecting malignancy by detecting the expression of different neurotrophic factors are distinct from each other, and it would be a serious burden to search all the different methods, because the searches for different neurotrophic factors are not co-extensive, in view that different neurotrophic factors are structurally and functionally different.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The response asserts that claim 6 has been amended to recite over- or under-expression as compared to expression of said neurotrophic factor measured in a normal subject.

The response has been considered but is not found to be persuasive for the following reasons:

Claims 6-9 are still indefinite, because claim 6 encompasses a method for diagnosis of malignancy, by detecting over- or underexpression of the neurotrophic factor NT-4/5, SEQ ID NO:45) in a sample. It is not clear in claim 6 how SEQ ID NO:45 could be both overexpressed and underexpressed in a sample.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 remain rejected under 112, first paragraph, for lack of enablement for a method for diagnosis of malignancy, for reasons already of record in paper of 03/08/07.

1) The nature of the invention

The response asserts that the nature of the claimed invention is routine in the art, requiring routine steps of contacting and detecting over- or under-expression of a neurotrophic factor.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the assertion, the claimed method is not routine, encompassing a method for diagnosing any pathological conditions, including any malignancy, any tumor or abnormal growths, or any pancreatic disease that over- or underexpresses a neurotrophic factor NT-4/5 (SEQ ID NO:45). However, there is no correlation between the claimed over- or underexpression of the neurotrophic factor NT-4/5 (SEQ ID NO:45) and a pathological condition, including any malignancy, any tumor or abnormal growths, or any pancreatic disease. Which pathological condition, which malignancy, which tumor or which pancreatic disease under- or over-expresses the claimed neurotrophic factor NT-4/5 (SEQ ID NO:45) is not predictable, nor disclosed in the specification, or in the art, other than the underexpression of NT-4 in pancreatic cancer, as detected by an anti-NT-4 antibody, as disclosed by Schneider et al, 2001.

2) The state of the prior art.

The response asserts that as acknowledged by the Examiner, the closest prior art detects the underexpression of NT-4 in pancreatic cancer, and thus supporting the enablement of the claims.

The response has been considered but is not found to be persuasive for the following reasons:

The art (Schneider et al) only teaches detecting of under-expression of NT-4 in pancreatic cancer, using an anti-NT-4 antibody, which is specific for NT-4.

The art does not support the enablement of the claims, because the art does not teach detection of any pathological condition, any malignancy, or any pancreatic disorder, by detecting over- or underexpresssion of NT4/5 (SEQ ID NO:45). Further, the art does not support the enablement of the claimed method, because different from using an antibody to the ligand NT-4, which is specific for NT-4, and does not require receptor-ligand binding, the claimed method uses the trkB receptor for detecting the ligand NT-4/5 (SEQ ID NO:45), which trkB receptor is not specific for the NT-4/5 (SEQ ID NO:45). That is, as disclosed in the specification (p.4, second paragraph), the TrkB receptor (SEQ ID NO:2) also binds to other ligands, the neurotrophic factors BDNF and NT-3, and thus is not specific. The level of a combination of all three neurotrophic factors, however, is not predictably to be the same as the level of the neurotrophic factor NT-4/5 (SEQ ID NO:45) alone, because the level of expression of a particular protein in a particular disease is unpredictable, in view of the teaching of Soontornniyooomkij et al and Guate et al, all of record. Further, not only the trkB receptor is not a specific probe, the ligand NT-4/5 (SEQ ID NO:45) is also not specific for the receptor trkB, because the receptor trkA also binds to the ligand NT-4/5 (the instant specification, p.4, second paragraph).

Moreover, concerning the species of pancreas cancer, since TrkA receptor also binds to the ligand NT-4/5 (SEQ ID NO:45) (the instant specification, p.4, second paragraph), and since

one cannot predict whether the endogenous ligand NT-4/5 (SEQ ID NO:45) at a reduced level in pancreas cancer is in free form or bound to the endogenous TrkA or TrkB3 receptor present in pancreas cancer (Schneider et al, of record, table 1 on p.1207), one cannot predict that the administered TrkB receptor (SEQ ID NO:2) is able to compete with and displace the endogenous TrkA receptor or TrkB3 receptor for binding and detecting the ligand NT-4/5 (SEQ ID NO:45) in an isolated tissue sample.

3) The relative skill of those in the art

The response asserts that the relative skill in the art is high. The response asserts that apparently, the USPTO suggests that the skill level may not be high, because the USPTO suggests that one cannot predict that the claimed neurotrophic factor is over- or underexpressed in a pathological condition. The response asserts that it would not be undue experimentation for one of skill in the art to practice the claimed invention, because detection of labeled polypeptide is well-known and routine in the art, and it is routine to measure the over- or underexpression of the the neurotrophic factor NT4/5.

The response has been considered but is not found to be persuasive for the following reasons:

The statement that "one cannot predict that the claimed neurotrophic factor is over- or underexpressed in a pathological condition, such as any malignancy, any abnormal growth, or any pancreatic disorder" does not suggest that the level of skill in the art is not high.

Further, although method of detection of labeled polypeptide is known in the art, the claimed method is not routine, because one cannot predict the level of the claimed neurotrophic

factor NT4/5 (SEQ ID NO:45) in a particular pathological condition, such as in a particular malignancy, or abnormal growth, or a particular pancreatic disorder, in view that expression level of a protein in a particular disease is unpredictable, as taught by Soontominiyooomkij et al. and Guate et al, and it would be undue experimentation for one of skill in the art to practice the claimed invention.

4) The unpredictability of the art

The response asserts that diagnostic methods are known in the art and are predictable; the application discloses the particular and novel aspects of the claimed methods, which are also predictable in that they rely on the disclosed sequences and are also based on methods and skills that are well-known in the art. The response assert that in addition, the application as filed explicitly discloses the pathological conditions to which the claimed diagnostic methods are directed; thus, the predictability of the art related to such diagnostic methods is quite high.

Concerning Soontominiyooomkij et al. and Guate et al., the response asserts that these references, directed to measurements of levels of neurotrophins and/or neurotrophin receptors, demonstrate that one of ordinary skill in the art would be able to practice and use the claimed methods, since these references discuss neurotrophin levels, using different methods, but showing that such measurements were possible and known to be of scientific and diagnostic value at the time .of the invention.

The response has been considered but is not found to be persuasive for the following reasons:

Although the specification discloses the structure of the neurotrophic factor NT- 4/5 (SEQ ID NO:45), and that a pathological condition could be diagnosed, by detecting the under-or overexpression of the neurotrophic factor NT- 4/5 (SEQ ID NO:45) (the instant specification, p.20, lines 20-25), however, other than the underexpression of NT-4 in pancreatic cancer, disclosed by Schneider et al, 2001, **which pathological conditions, which malignancy, which tumor or which pancreatic disease under- or over-expresses the claimed neurotrophic factor NT-4/5 (SEQ ID NO:45) is not disclosed in the specification, nor predictable**.

Further, although the method for measuring the level of a protein is routine in the art, one cannot predict the level of expression of the claimed neurotrophic factor NT4/5 (SEQ ID NO:45) in a particular pathological condition, such as in a particular malignancy, or abnormal growth, or a particular pancreatic disorder, because the expression level of a protein in a particular disease is unpredictable, in view of the teaching of Soontornniyooomkij et al and Guate et al, all of record. Soontornniyomkij et al, 1999 (Acta neuropathologica 98(4): 345-8) teach that expression of trkB proteins is characteristic of particular disease processes, as shown by the absence of BDNF and trkB protein in glia cells in AD patients, in contrast to their presence in HIV patients (abstract, last seven lines). Similarly, Guate et al, 1999 (BJU Internatl, 84: 495-502) teach that trkA and TrkC are overexpressed in prostate cancer, as compared to normal prostate tissue, while trkB is not detected in prostate cancer (abstract, p.496, second column, last paragraph).

Moreover, the claimed probe, trkB receptor, would be non-specific, binding also other neurotrophic factors, supra, and therefore, one cannot predict that the level of the specific NT-4/5 (SEQ ID NO:45) would not be interfered by the presence of other neurotrophic factors. Further, concerning the species of pancreas cancer, one cannot predict that the trkB receptor is a suitable

probe for the following reasons: It is note that although trkB receptor is not detected in pancreas cancer, TrkA and trkB3 receptors are detected (Schneider et al, of record, table 1 on p.1207). Since TrkA receptor also binds to the ligand NT-4/5 (SEQ ID NO:45) (the instant specification, p.4, second paragraph), and since one cannot predict whether the endogenous ligand NT-4/5 (SEQ ID NO:45) at a reduced level in pancreas cancer is in free form or bound to the endogenous TrkA or TrkB3 receptor also present in pancreas cancer (Schneider et al, of record, table 1 on p.1207), one cannot predict that the administered TrkB receptor (SEQ ID NO:2) is able to compete with and displace the endogenous TrkA receptor or TrkB3 receptor for binding and detecting the ligand NT-4/5 (SEQ ID NO:45) in an isolated tissue sample.

Moreover, one cannot predict that the truncated intracellular domain of trkB receptor, SEQ ID NO:4 (see figure 1B legend on page 3 of the instant specification), even binds to the ligand neurotrophic factor NT-4/5 (SEQ ID NO:45), in view that one cannot predict that SEQ ID NO:4 retains the binding region for the ligand SEQ ID NO:45, and in view that not any region of a receptor binds to its ligand.

5) The breadth of the claims

The response asserts that the claims are limited to the pathological conditions, whether it is a malignancy, a tumor or a pancreatic disorder, to be diagnosed be one that is characterized by the over- or undeexpression of a neurotrophic factor.

The response has been considered but is not found to be persuasive for the following reasons:

The claims are broad, because they encompass diagnosis of a genus of numerous possible pathological conditions, or malignancy, or tumor or pancreatic disorder that under- or overexpress the neurotrophic factor NT-4/5.

6) The amount of direction and the absence of working example.

The response asserts that the instant application teaches how to measure levels of neurotrophins of interest in tissue using the novel trkB polypeptides of the claims. The response asserts that in addition, the scientific literature demonstrates that neurotrophin measurements were possible by other means as well (see, for example, the references cited by the USPTO, including, for example, Soontorniniyooomkij et al.).

The response has been considered but is not found to be persuasive for the following reasons:

Although the specification and the art discloses how to measure the level of the neurotrophic factor, the specification does not disclose, nor having any concrete evidence of which diseased tissue or which disease under- or overexpresses the claimed neurotrophic factor, as compared to the normal corresponding control. The specification does not have any data, or concrete evidence that the trkB receptor is a suitable probe, and could bind specifically to the ligand NT-4/5 (SEQ ID NO:45) in the presence of endogenuous trkB receptor and truncated forms thereof.

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the

claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS

September 06, 2007

/Larry R. Helms/

Supervisory Patent Examiner